

efficiency, a cellular phone reporting programme was also integrated into the system after the earthquake in Sichuan province in 2008. Local hospitals report incident cases of scarlet fever to the national and provincial Centers for Disease Control and Prevention (CDC). Additionally, the Chinese Government strengthened its overall public health disease surveillance following the establishment of the national surveillance system with a ten-fold increase in public health funding. The surveillance system covers 39 notifiable infectious diseases, which are divided into three classes—A, B, and C. As a class B infectious disease, scarlet fever incidence should be reported to the network within 24 h of diagnosis. If a high incidence of scarlet fever was indicated in a particular region, the national and local CDC should collaborate to take appropriate measures to isolate the infected individuals. Moreover, the surveillance system would provide a more standardised and comprehensive description of scarlet fever, and aggregated data from the system would allow further examination of potential patient characteristics that are associated with the disease,^{8–10} including long-term patterns, seasonality, and spatial features. These data would provide reference values to better understand the disease and inform public health decision making. Although surveillance systems have progressed in the past decade, they can still be improved. The current surveillance system in China collects several patient sociodemographic characteristics, including age, sex, occupation, living address, and the hospital to which they reported. However, data on clinical characteristics, such as laboratory test results, should also be included in the future.

In response to the resurgence of scarlet fever, the Chinese Government has taken measures for disease control and prevention. Those measures include improving diagnosis of the disease, strengthening

surveillance among school students, and establishing an improved and efficient epidemic response to scarlet fever outbreaks. Given the establishment of the universal two-child policy and the ageing population, the distribution of age in China's population is gradually changing.⁶ The spectrum of infectious diseases could also change as a result. Age-related infectious diseases like scarlet fever should be better monitored by way of national surveillance systems. The surveillance system will have a crucial role in the prevention and control of infectious disease.

Xingyu Zhang, *Yan-Cun Liu

Department of Surgery, Emory University School of Medicine, Atlanta, GA, USA (XZ); and Department of Emergency Medicine, Tianjin Medical University General Hospital, Tianjin 300052, China (Y-CL)
yancunliu@gmail.com

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Reappraising the cardiosafety of dihydroartemisinin-piperaquine

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The arsenal of efficacious drugs for the treatment of malaria remains small and is clearly insufficient to tackle the global burden of malaria, with more than 216 million clinical episodes and nearly half a million deaths annually.¹ Among the new antimalarials that have been developed in the past decade, the artemisinin-based combination dihydroartemisinin-piperaquine is one of

the most promising, on account of its good efficacy and tolerability, simplified dose schedule (ie, once daily for 3 days), and long post-treatment prophylactic effect.² The only brand of dihydroartemisinin-piperaquine that has been registered under stringent regulatory authority is Eurartesim (licensed by the European Medicines Agency [EMA] in 2011), although at least three other

brands exist: Duo-cotecxin (also prequalified by WHO), D-ARTEPP, and Arterakine. Dihydroartemisinin-piperaquine is not only used as a treatment of uncomplicated malaria but also has been proposed as an alternative to sulphadoxine-pyrimethamine for intermittent preventive treatment of malaria during pregnancy,³ or as a suitable drug for the mass treatment of entire populations as part of malaria-elimination endeavours.⁴

However, because piperaquine can cause a dose-dependent effect on cardiac repolarisation, which can manifest as a prolonged QT interval in surface electrocardiograms (ECG), concerns have been raised regarding the cardiosafety of dihydroartemisinin-piperaquine, which have limited its much wider deployment and use. Indeed, such potentially pro-arrhythmogenic characteristics, which theoretically could be linked to an increased risk of ventricular fibrillation and sudden death, led the EMA to recommend that an ECG should be done before the drug's administration, that the drug should be administered under strict fasting conditions (because food increases piperaquine's plasma concentration), and that repeated doses should be limited in number and frequency.⁵ These recommendations reduced the potential use of the drug in most areas of the world where malaria remains highly endemic. Dihydroartemisinin-piperaquine has since become one of the most studied drugs in relation to its associated repolarisation-related cardiotoxicity, conditions that were not applied to other antimalarial drugs with similar potential (quinine, amodiaquine, or chloroquine) when they were licensed, more than half a century ago.

Although the occurrence of clinically relevant adverse cardiovascular effects associated with dihydroartemisinin-piperaquine or piperaquine on its own after several years of extensive use seems rare, the drug's association with life-threatening cardiac events remains unchallenged. In this issue of *Lancet Infectious Diseases*, Xin Hui S Chan and colleagues⁶ present the results of a systematic review and meta-analysis of 94 studies including nearly 200 000 pooled individuals given dihydroartemisinin-piperaquine for several indications, including treatment of uncomplicated malaria, intermittent preventive treatment, and mass drug administration. The investigators compared the risk of sudden unexplained death after

dihydro-artemisinin-piperaquine with the baseline rate of sudden cardiac death in a reference population aged younger than 35 years, chosen to reflect the typical age of antimalarial users in malaria-endemic areas.

The median pooled risk estimate of sudden unexplained death after dihydroartemisinin-piperaquine was 1 in 757 950 (95% CI 1 in 2 854 490 to 1 in 209 114), a finding deemed to be similar (and not higher) than the baseline rate of sudden cardiac death in the reference population after standardisation to 30-day risks (0.7–11.9 per 100 000 person-years or 1 in 1714 280 to 1 in 100 835). The investigators also examined the 61 deaths of individuals in the studies who received the drug, 31 of which occurred during the 3-day treatment period, and a further 30 that occurred during one terminal elimination half-life of piperaquine (around 30 days). Members of a WHO Expert Review Group, specifically convened to review the cardiosafety of antimalarial drugs,⁷ concluded that only one of these deaths (of a healthy woman aged 16 in Mozambique who developed heart palpitations several hours after the second dose of dihydroartemisinin-piperaquine and collapsed and died on the way to hospital) was consistent with sudden cardiac death and possibly causally related to drug exposure. Although under-reporting is likely, that only one death among nearly 200 000 studied individuals could be linked to the drug strongly supports the idea that sudden deaths potentially attributable to repolarisation-related tachyarrhythmia after treatment with dihydroartemisinin-piperaquine are infrequent.

These reassuring data further corroborate the conclusions of the aforementioned WHO expert panel,⁷ of findings from a previous smaller systematic review and meta-analysis on this subject,³ and of various surveillance efforts undertaken by many independent research groups to study the safety of dihydroartemisinin-piperaquine.^{2,8–10} Additionally, a multicentre clinical trial in five sub-Saharan African countries of a new dispersible paediatric formulation of dihydroartemisinin-piperaquine in infants aged 6–12 months did not note any clinical cardiosafety concerns.¹¹ Further studies (NCT02605720) assessing the safety in healthy individuals (including detailed ECG assessment) of cumulative repeated monthly treatment with dihydroartemisinin-piperaquine, mimicking regimen used in mass-drug administration are underway.

Reappraising the value of the few available effective antimalarials is more important now than ever. The global effort against malaria is at a crossroads;¹² malaria incidence seems to be rising again after many years of decreases. Dihydroartemisinin–piperaquine should be shed of its cardiotoxic reputation, so that malaria-endemic areas can benefit from its full potential and to decrease the toll that malaria still imposes globally.

*Pere Millat-Martínez, *Quique Bassat*

Barcelona Institute for Global Health, ISGlobal, Hospital Clínic Universitat de Barcelona, Barcelona, 08036, Spain (PM-M, QB); Lihir Malaria Elimination Programme (LMEP), Lihir Island, New Ireland Province, Papua New Guinea (PM-M); Centro de Investigação em Saúde de Manhiça, Maputo, Mozambique (QB); ICREA, Pg. Lluís Companys 23, 08010 Barcelona, Spain (QB); and Pediatric Infectious Diseases Unit, Pediatrics Department, Hospital Sant Joan de Déu (University of Barcelona), Barcelona, Spain (QB). quique.bassat@isglobal.org

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HRP-2 deletion: a hole in the ship of malaria elimination

Malaria remains a major health challenge in tropical and subtropical countries with an estimated incidence of 216 million cases and 445 000 deaths worldwide in 2016. Every 2 minutes a child under 5 years old dies because of malaria. India accounts for 80% of malaria cases and 60% of malaria deaths in the southeast Asia region (SEAR).¹ *Plasmodium falciparum* malaria constitutes 63·4 % of total malaria cases in India. More than 90% of malaria cases in India are reported from remote, difficult to reach rural and tribal areas, where the diagnosis of malaria is a challenge in resource-limited settings.

Malaria rapid diagnostic tests (RDTs) have been extensively used as diagnostic tools because of their ease of handling and quick results. The sale of about 1·66 billion malaria RDTs across the globe during

2010–16 speaks volumes about their utility.¹ Improved sensitivity and heat stability makes *P falciparum*-histidine rich protein (HRP) 2 based RDTs the preferred choice for timely diagnosis of falciparum malaria in remote areas with poor health-care infrastructure. Berhane and colleagues have shown high prevalence (41–80%) of HRP2 gene deletion in *P falciparum* and high frequency of false negative RDT results, irrespective of parasite densities, in a hospital-based study in Eritrea.² At a time when India and several other countries in SEAR are accelerating the pace of malaria control programmes to achieve the goal of malaria elimination by 2030, the deletion of HRP2 is a matter of serious concern, since RDTs are the mainstay diagnostic tool for community surveys, along with microscopy in hospitals. The diverse ecological conditions, difficult